Attorney Docket # 5482-2 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Yuen-Liang LAI et al.
Serial No.: 10/803,666
Filed: March 18, 2004
For: Use of Arsenic-Containing Pharmaceutical Composition in Combination with Radiation Therapy for Cancer Treatment

Examiner: Pak, John D
Group Art: 1616

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Name of applicant, assignee or Registered Representative

Signature

Date of Signature

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Commissioner for Patents
P.O. Box 1450
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DECLARATION of Yuen-Liang Lai, Yu-Jen Chen, Yu-Fang Hu, Chi-Liang Kan, and Kuang-Chun Chiu under 37 C.F.R. § 1.132

We, Yuen-Liang Lai, Yu-Jen Chen, Yu-Fang Hu, and Chi-Liang Kan, and Kuang-Chun Chiu do hereby declare as follows:

1. We are the original sole inventors and applicants of U.S. Patent Application Serial No. 10/803,666. We have read the specification of U.S. Patent Application Serial No. 10/803,666. We have also read the Office Action dated March 21, 2007 related to this U.S. Patent Application and one of the references cited by the examiner, which is Lai et al. (Anti-Cancer Drugs, 2003, vol. 14, pages 825-828, accepted for publication on September 3, 2003).

2. We are the original and sole inventors of every claim in the specification of U.S. Patent Application Serial No. 10/803,666. Other than us, none of other co-authors of the Lai et al., i.e., Hen-Hong Chang, Ming-Jer Huang, Kou-Hwa Cahng, Wen-Hao Su, Hong-Wen Chen, Chang-Hung Chung, We-Yu Wang, and Li-Huan Lin, is an inventor or a co-inventor of any claim in U.S. Patent Application Serial No. 10/803,666. These non-inventor authors only worked under our direction to test the effectiveness and safety of the presently claimed invention and did not make any inventive contribution to the present invention.

3. We further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed and declared at Taiwan this 11 of June 2007.

Yuen-Liang Lai

Yu-Jen Chen

Yu-Jen Chen

Yu-Feng Hu

Chi-Liang Kan

Kuang-Chun Chiu

2. We are the original and sole inventors of every claim in the specification of U.S. Patent Application Serial No. 10/803,666. Other than us, none of other co-authors of the Lai et al., i.e., Hen-Hong Chang, Ming-Jer Huang, Kou-Hwa Cahng, Wen-Hao Su, Hong-Wen Chen, Chang-Hung Chung, We-Yu Wang, and Li-Huan Lin, is an inventor or a co-inventor of any claim in U.S. Patent Application Serial No. 10/803,666. These non-inventor authors only worked under our direction to test the effectiveness and safety of the presently claimed invention and did not make any inventive contribution to the present invention.

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Signed and declared at Taiwan this ____ of June 2007.

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Yuen-Liang Lai

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Yu-Jen Chen

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Yu-Fang Hu

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Chi-Liang Kan

_____ 6/1/2007
Kuang-Chun Chiu

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Signed and declared at Taiwan this ____ of June 2007.

Yuen-Liang Lai

Yu-Jen Chen

Yu-Fang Hu

Chi-Liang Kan

Kuang-Chun Chiu

PATENT

DOCKET NO.: CP380C
Application No.: 10/649,776
Office Action Dated: December 15, 2005

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (currently amended) A method of treating melanoma in a human, which comprises administering parenterally a therapeutically effective amount of ~~one or more arsenic compounds~~ arsenic trioxide to said human.

2. (canceled)

3. (currently amended) The method of ~~claim 2~~ claim 1, wherein said arsenic trioxide is formulated as an ionic aqueous solution.

4. (original) The method of claim 1, wherein the total daily amount administered is from about 10 μg to about 200 mg.

5. (original) The method of claim 1, wherein the total daily amount administered is from about 0.5 mg to about 150 mg.

6. (original) The method of claim 1, wherein the total daily amount administered is from about 0.5 mg to about 70 mg.

7. (currently amended) The method of claim 1, wherein the arsenic ~~compound~~ trioxide is administered intravenously.

8. (currently amended) The method of claim 1, wherein the arsenic ~~compound~~ trioxide is administered in combination with an effective amount of at least one other therapeutic.

9. (original) The method of claim 8, wherein the other therapeutic agent is a chemotherapeutic or radiotherapeutic.

10. (original) The method of claim 8, wherein the other therapeutic agent is selected from the group consisting of etoposide, cisplatin, carboplatin, estramustine phosphate, vinblastine, methotrexate, hydroxyurea, cyclophosphamide, doxorubicin, 5-fluorouracil, taxol, diethylstilbestrol, VM-26(vumon), BCNU, all-trans retinoic acid, procarbazine, cytokines, therapeutic vaccines, and immunomodulators.

11. (canceled)

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PATENT

REMARKS

Following entry of the foregoing amendments, claims 1 and 3 to 10 will be pending in the application. Claims 3, 7, and 8 have been amended, and claims 2 and 11 have been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed. No new matter has been added.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

Claims 1 to 11 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chinese Patent number CN 1079391 ("the 391 patent") in view of U.S. Patent No. 6,720,011 ("the Zhang patent") and Shimotsuura, S., *Journal of Tokyo Dental College Society*, 1986, 86(8) 1237-1253 ("the Shimotsuura article"). Applicants respectfully request reconsideration and withdrawal of the rejection because the office action has failed to establish *prima facie* obviousness.

To establish *prima facie* obviousness, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). And the proposed modification or combination of the prior art ***must have had a reasonable expectation of success***, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

"[W]hether a particular combination might be 'obvious to try' is not a legitimate test of patentability." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). "Obvious to try" situations arise where it might have been obvious to "explore a new technology or general approach that seemed to be a promising filed of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re*

O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988). *See also Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.ed. 1367, 1380 (Fed. Cir. 1986)(stating that "At *most*, these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished.")(emphasis in original).

Upon review of the references cited in the Office action, those skilled in the art would not have reasonably expected at the time of the invention that arsenic trioxide could have been successfully used to treat melanoma in humans. At most, it might have been obvious to persons skilled in the art ***to try*** to use arsenic trioxide to treat melanoma, but much more is required to establish *prima facie* obviousness.

The 391 patent describes the treatment of "skin cancer" and "body surface tumors" with a combination of arsenic trioxide and traditional Chinese medicines. As pointed out in the Office action, the patent does not describe treatment of ***melanoma*** with arsenic trioxide, however.[1]

The Zhang patent describes arsenic trioxide compositions[2], but fails to provide any guidance whatsoever as to the efficacy of the compositions for melanoma treatment. The patent's single working example describes the use of arsenic trioxide compositions for the treatment of a particular type of leukemia (acute promyelocytic leukemia) (col. 2. ln. 59 to col. 3, ln. 27). In addition, the patent's description of the effect of the described arsenic trioxide compositions on cancer cells is limited to a description of its effect on leukemia cells:

> Laboratory experiments indicate that the composition shows a strong abruptive effect on the membranes of leukemic cells. It also inhibits DNA/RNA synthesis in such cells, reduces the rate of proliferation of leukemic cells and destroys the leukemic cells.

(col. 2, lns. 23 to 27).

The Shimotsuura article describes the efficacy of arsenic trioxide in a mouse sarcoma model and indicates that arsenic trioxide was only efficacious when it was coadministered with an antidote. The article fails to describe or suggest the treatment of melanoma with arsenic trioxide. Although the Office action asserts that the article teaches that "antineoplasmic [*sic*]

[1] Office action dated December 15, 2005, page 3.
[2] "The present invention is directed to an intravenous drip composition for the treatment of cancers. The cancers treatable include leukemia, hepatoma and lymphoma." (col. 1, lns. 33 to 35).

actions of arsenic trioxide are primarily achieved by DNA composition blockage,"[3] the article states that the DNA composition blockage occurred in the S-180 (sarcoma) cells transplanted into the mice, and does not teach that DNA composition blockage occurs in cancerous cells other than sarcoma cells:

> From above results, As_2O_3 is considered that can increase life span of the mouse by blocking DNA composition of S-180 cells and protein composition.[4]

The references cited in the Office action thus fail to teach or suggest that arsenic trioxide can be successfully used to treat melanoma in humans. Rather, the references teach that arsenic trioxide has been used in humans to treat unspecified "skin cancer" and acute promyelocytic leukemia and suggest that it may be effective against sarcomas when administered in conjunction with an antidote.

As understood by those skilled in the art at the time of the invention, there are many different types of skin cancer, and different approaches are taken towards treating different types of skin cancer. For example, the most common types of skin cancer are basal cell carcinoma and squamous cell carcinoma.[5] Other types of skin cancer include melanoma, cutaneous T-cell lymphomas, Kaposi's sarcoma, extramammay Paget's disease, apocrine carcinoma of the skin, and metastatic malignancies from various primary sites.[6] Those skilled in the art would have appreciated at the time of the invention that the efficacy of a particular anti-cancer agent against a specific type of cancer was not predictive of its efficacy against other types of cancers. It was understood that "[i]ncreasingly disease-specific therapies are being developed that will have optimum application for only one tumor type, although representing ineffective and toxic treatment for others."[7] Indeed, the therapeutic agents most commonly used to treat cancers at the time of the invention (and at present, as well) were effective only against specific types of cancers, and generally did not exhibit broad efficacy against numerous cancer types.[8] Accordingly, those skilled in the art would not have reasonably expected that arsenic trioxide

[3] Office action dated December 15, 2005, page 3.
[4] Page 20 of the English translation.
[5] National Cancer Institute Website (copy enclosed as Exhibit A).
[6] *Id.*
[7] *Medical Oncology*, Calabresi, P., *et al.*, eds., 1985, Macmillan Publishing Company, page 257 (copy enclosed as Exhibit B).
[8] *Id.* at 295-297 (copy enclosed as Exhibit B.)

could have been successfully used to treat melanoma in humans just because it had been reported to have efficacy against an unspecified type of skin cancer. Although those skilled in the art might arguably have considered trying to use arsenic trioxide to treat melanoma, the results of doing so could not have been predicted with a reasonable degree of certainty. Accordingly, those skilled in the art at the time of the invention would not have reasonably expected that arsenic trioxide could have been successfully used to treat melanoma in humans.

The Office action asserts that "[b]ecause melanoma is an uncontrolled growth of cells, one having ordinary skill in the art would have been motivated to administer arsenic trioxide to treat such uncontrolled growth of cells, particularly in view of its adverse effect on rapid DNA replication."[9] However, as discussed above, even if those skilled in the art would have been so motivated, they would not have had a reasonable expectation of success for such an endeavor. The Office action appears to be asserting that those skilled in the art would have been motivated to use arsenic trioxide to treat any type of uncontrolled cell growth. Due to the nature of cancer, and methods for its treatment and management at the time of the invention, however, those skilled in the art would not have reasonably expected that an agent shown to be effective against an unspecified type of skin cancer could have been successfully used to treat melanoma in humans. As discussed above, there are many types of skin cancers, and different approaches have been taken for treating different types of skin cancers. For example, the most common types of skin cancer, basal cell carcinoma and squamous cell carcinoma, are treated by topical application of 5-fluorouracil.[10] In contrast, melanoma is not typically treated by topical application of a chemotherapeutic, but is treated by systemic administration of carmustine, dacarbazine, interferon-α, or hydroxyurea.[11] Different types of skin cancers are thus treated differently, and the reported use of arsenic trioxide to treat unspecified "skin cancer" would not have led those skilled in the art to reasonably believe that melanoma could have been successfully treated with arsenic trioxide.

[9] Office action dated November 18, 2005, page 4.
[10] National Cancer Institute Website (copy enclosed as Exhibit C).
[11] *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, Ninth Edition, Hardman J.G., *et al.*, eds., 1996, McGraw-Hill, page 1227 (copy enclosed as Exhibit D).

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Applicants respectfully submit, therefore, that the Office action has failed to establish *prima facie* obviousness, and Applicants, accordingly, respectfully request withdrawal of the rejection.

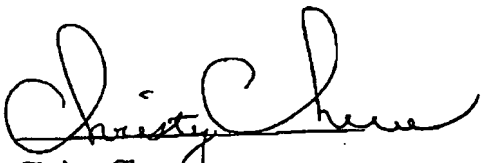
Information Disclosure Statement

In response to the Examiner's request for clarification as to which of the search reports cited in the Form PTO 1449 was issued in connection with the corresponding European application, the "International Search Report of EP 03019629"[12] was issued in connection with the counterpart European application.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,



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[12] The Form PTO 1449 incorrectly states that the application number of the corresponding European application is "EP 03019628."

3. (Amended) A method of treatment of melanoma, breast, colon, ovarian, renal, central nervous system, bladder, prostate or lung cancer in a human in need of such treatment, which comprises administering a therapeutically effective amount of one or more arsenic compounds to said human.

9. (Amended) The method of claim 4 wherein said tumor of the central nervous system is selected from the group consisting of neuroblastoma, retinoblastoma, glioblastoma and oligodentroglioma.

13. (Amended) A method for treatment of neoplastic diseases in a human in need of such treatment, which comprises administering to said human an effective amount of an arsenic compound, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of at least one other therapeutic agent.

14. (Amended) The method of claim 13 in which said other therapeutic agent is a chemotherapeutic agent or radiotherapeutic agent.

15. (Amended) The method of claims 1, 2, 3, or 13 in which said administration is made parenterally, topically, dermally, directly into the tumor or orally.

16. (Amended) The method of claim 13 in which said other therapeutic agent is selected from the group consisting of etoposide, cisplatin, carboplatin, estramustine phosphate, vinblastine, methotrexate, hydroxyurea, cyclophosphamide, doxorubicin, 5-fluorouracil, taxol, diethylstilbestrol, VM-26 (vumon), BCNU, all-trans retinoic, acid, procarbazine, cytokines, and therapeutic vaccines.

17. (Amended) The method of claim 1, 2, 3 or 13 in which said administration is made via an implantation device.

18. (Amended) A method of treatment of hematopoietic disorders in a human in need of such treatment, which comprises administering one or more arsenic compounds to said human, wherein said hematopoietic disorder is selected from the group consisting of acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, myeloid metaplasia, myeloid dysplastic syndrome, multiple myeloma and plasmacytoma.

Please add the following claims:

21. (New) The method of claim 1, wherein arsenic trioxide is administered intravenously in a total daily dose of from 0.5 mg to 150 mg.

22. (New) The method of claim 2, wherein arsenic trioxide is administered intravenously in a total daily dose of from 0.5 mg to 150 mg.

23. (New) The method of claim 3, wherein arsenic trioxide is administered intravenously in a total daily dose of from 0.5 mg to 150 mg.

24. (New) The method of claim 1, 2, or 3, wherein the arsenic compound is an arsenic halide.

25. (New) The method of claim 1, 2, or 3, wherein the arsenic compound is an arsenic sulfide.

26. (New) The method of claim 1, 2, or 3, wherein the arsenic compound is an organic compound.

27. (New) The method of claim 1, 2, or 3, wherein the arsenic compound is administered as a prodrug.

28. (New) The method of claim 1, 2, or 3, wherein the arsenic compound is administered orally.

29. (New) The method of claim 1, 2, or 3, wherein the arsenic compound is administered as a pill or tablet.

REMARKS

Claims 1-20 are pending and have been rejected. Minor editorial amendments have been made to claims 1, 2, 3, 9, and 13-18. Claims 19 and 20 have been canceled. Claims 21-23 have been added, based on the specification, for example, at page 25, lines 20-23. Claims 24-27 have been added, based on the specification, for example, at page 15, lines 14-17 and 28-31. Claims 28 and 29 have been added, based on the specification, for example, at page 21, line 30 to page 22, line 14. Claims 1-18 and 21-29 remain in the case.

Claims 1-20 stand rejected under the second paragraph of Section 112. The claims have been amended to address the points raised by the examiner.

Claims 19 and 20 are rejected under Section 102(b) or, in the alternative, under Section 103(a) over any of Chen *et al.*, *Blood* 88: 1052 (Aug. 1996), Shen *et al.*, *Blood* 89: 3354 (May 1997), and Zhang *et al.*, translation of *Chinese J. Hematology* (Feb. 1996), volume 17. Claims 19 and 20 have been canceled.

Claims 1-20 are rejected under Section 103(a) based on the combined teachings of Shimotsuura *et al.*, Shen *et al.*, Chen *et al.*, Zhu *et al.*, Sun *et al.*, and Zhang *et al.*

All of the cited documents disclose the treatment of acute promyelocytic leukemia (APL) with either (1) arsenic trioxide, or (2) a composition which contains arsenic stone and HgCl, along with other ingredients. Shimotosuura *et al.* report on studies on the antineoplastic action of arsenic trioxide in a mouse model. Shen *et al.* discloses the use of arsenic trioxide in the treatment of 15 relapsed patients with APL. Chen *et al.* discloses *in vitro* studies in NB_4 cells, leading to a discussion of possible cellular and molecular mechanisms of arsenic trioxide in the treatment of APL. Zhu *et al.* discloses arsenic-induced PML targeting onto nuclear bodies. Sun *et al.* discloses treatment of 32 cases of APL, denoted acute early granulocytic leukemia in the translation. Zhang *et al.* discloses the treatment of 72 cases of APL.

None of the cited documents makes any disclosure that would lead the skilled artisan to use an arsenic compound to treat cancers other than APL, such as

(1) a solid tumor, as claimed in claim 1,

(2) metastatic neoplastic disease, as claimed in claim 2,

(3) melanoma, breast, colon, ovarian, renal, central nervous system, bladder, prostate or lung cancer, as claimed in claim 3, and

(4) a hematopoietic disorder other than APL, selected from the group consisting of acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, myeloid metaplasia, myeloid metaplasia, myeloid dysplastic syndrome, multiple myeloma and plasmocytoma.

In the first instance, positive results in treating APL would not have led a skilled artisan to predict similar results when treating such diverse cancers as solid tumors, metastatic neoplastic disease, or any of the cancers listed in (3) above. Nor would such results have suggested the use of an arsenic compound in the treatment of the other hematopoietic disorders listed in (4) above.

Indeed, the art as a whole, including several of the cited documents, contains teachings that would have led a skilled artisan to conclude that an arsenic compound would not be effective in treating these different categories of neoplasia. Rather, the art taught that arsenites are highly toxic compounds which actually could ***cause*** cancer. Because of this toxicity and the ability to cause cancer, arsenic compounds had been discarded as potential anti-cancer drugs.

For example, when used in animals, high concentrations of inorganic arsenic given by intraperitoneal (IP) injection caused damage to target enzymes and marked toxicity. In fact, the experimental results in mice that are reported starting on page 10 of Shimotosuura *et al.* actually show a minimal improvement in survival, at best, and in many instances a actual ***decrease*** in life span for most of the arsenic trioxide compositions and concentrations administered.

More specifically, when arsenic trioxide 5 mg/kg was given by IP injection, there was only a 10.4% improvement in survival as compared to untreated mice (Table 1). This minimal improvement in survival is insignificant, and arsenic trioxide was considered to be an inactive drug according to the criteria for new cancer drugs outlined by the World Health Organization, which requires a greater than 25% improvement in survival before a

drug is considered to be "effective." Indeed, more favorable results in increasing life span were generated in Shimotosuura when arsenic trioxide was administered in combination with an arsenic ***antidote***, such as 2,3-dimercapto-1-propane-sulfonic acid (DMPS) or meso-2,3-dimercaptonecinic acid (DMSA), suggesting that the arsenic compounds did not improve survival rates in the mice. Moreover, the mouse model used in Shimotosuura *et al.* is not considered by those of ordinary skill in this art to be predictive of efficacy in humans. Thus, both the lack of predictability of the mouse model and the actual results achieved with that model in Shimotosuura *et al.* are factors which would have led a skilled artisan to discount the value of arsenic compounds in the treatment of neoplasias as presently claimed.

In this same vein, Sun *et al.* suggests that arsenic must be used in combination with arsenic antidotes, and with other toxic agents, in order to achieve positive results. Sun *et al.* used Ai-Ling No. 1, a combination of arsenic stone or arsenic sublimate and HgCl. See paragraph 9 of the Rule 132 declaration of Guo-Qiang Chen that was submitted in SN 08/702,011 (copy appended). The arsenic and mercury compounds were administered "in combination with the Chinese medical practice of administering the treatment according to the pattern." This entails the co-administration of numerous other ingredients to counteract the effects of the arsenic, including Ginseng and Astragalus Four Agents Decoction, Ginseng White Tiger Decoction and Bone-Clearing Powder, Antelope Horn and Forsythia Toxin-Resolving Decoction, Heart-Draining Decoction or Gentian Liver-Draining Decoction, Construction-Clearing Decoction, and Bone-Clearing Powder and Pulse-Engendering Powder. This teaching would not have led a skilled artisan to conclude that it was an arsenic compound that led to the positive results reported.

Even those documents which do suggest that arsenic trioxide is the active ingredient in achieving positive results in the treatment of APL would not have led a skilled artisan to the conclusion that an arsenic compound might have positive effects in treating ***other*** neoplasias. For example, Zhu *et al.* disclose that APL is associated with the t(15:17) translocation, which generates a PML/RARα fusion protein between PML, a growth suppressor localized on nuclear matrix-associated bodies and RARα, a nuclear receptor for retinoic acid (RA). Based on their results, Zhu *et al.* conclude that in APL cells, arsenic targets PML and PML/RARα onto nuclear bodies (NB) and induces their degradation.

Similarly, Chen *et al.* posit that arsenic trioxide induces NB_4 cell apoptosis with down-regulation of Bcl-2 expression and modulation of PML proteins. The art thus identifies a particular mechanism, ***specific to APL and APL cells***, by which arsenic exerts its effects. In light of this specific mode of action, a skilled artisan would not have predicted that arsenic compounds would have been effective in treating the other neoplasias as recited in applicants' claims.

Despite these teachings in the art, Examiner Pak urges that, "while the references do not expressly disclose the treatment of practically all cancer types, as claimed, one having ordinary skill in the art would have been motivated to utilize arsenic compounds such as arsenic trioxide to treat solid tumors and other neoplastic diseases as claimed herein because arsenic compounds have been taught to possess antineoplastic properties, in addition to having been clinically demonstrated as being effective in treating leukemia." This broad-brush approach contrasts sharply with the examiner's treatment of an earlier application, U.S. serial No. 08/702,011, which applicants make of record in an information disclosure statement filed herewith, and which, at one time, included claims to treating "cancer" with arsenic trioxide. (The '011 application embodies the results of two publications cited by the examiner, Shen *et al.* and Chen *et al.*) In relation to the "cancer treatment" claims of the '011 application, Mr. Pak argued that enablement was lacking because "broad cancer treatment is claimed when only one type of cancer is shown to be treated...however, in the field of treating cancer, no one substance has been found that successfully treat[s] all types of cancer." Thus, the examiner discounted the predictive value of a showing for one cancer type, relative to the efficacy of arsenic trioxide, but now exalts the predictive value of the same showing!

In any event, the prior art in question illuminates a very specific mechanism for the effect of arsenic on APL. Given so narrow a teaching, one of ordinary skill would not "have been motivated to use arsenic compounds such as arsenic trioxide" (in the examiner's words) to treat cancers other than APL. In contrast, applicants have shown positive results, wholly unexpected, against a wide variety of cell lines in the National Cancer Institute tumor cell line-screening system. These results in the specification clearly show that an arsenic compound was effective in inhibiting growth in cell lines of many common forms of cancer. This is very significant in view of the high correlation between drug anti-tumor

activity in the NCI system and subsequent clinical effect in patients. Indeed, this screening approach identified taxol as applicable to a variety of cancers, and subsequent clinical results validated the broad anti-cancer activity of taxol.

Finally, the combined teachings of the cited documents would not have led a skilled artisan to combine another therapeutic agent with an arsenic compound in the treatment of neoplastic diseases as claimed in claim 13, and particularly with a chemotherapeutic or radiotherapeutic agent, as claimed claim 14. There is no suggestion that any benefit might accrue to combinations with other therapeutic agents, particularly with chemotherapeutic or radiotherapeutic agents as recited in claim 14, or the specific therapeutic agents recited in claim 16.

In view of the foregoing amendments and remarks, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully requested. Should there be any questions regarding this application, the examiner is invited to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

August 21, 2001
Date

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MARKED-UP VERSIONS OF AMENDED CLAIMS

1. (Amended) A method of [treating] treatment of solid tumors in a [mammal] human in need of such treatment, which comprises administering a therapeutically effective amount of one or more arsenic compounds to said [mammal] human.

2. (Amended) A method of [treating] treatment of metastatic neoplastic disease in a [mammal] human in need of such treatment, which comprises administering a therapeutically effective amount of one or more arsenic compounds to [a mammal in need of such therapy] said human.

3. (Amended) A method of [treating] treatment of melanoma, breast, colon, ovarian, renal, central nervous system, bladder, prostate or lung cancer in a human in need of such treatment, which comprises administering a therapeutically effective amount of one or more arsenic compounds to said human.

9. (Amended) The method of claim 4 wherein said tumor of the central nervous system is selected from the group consisting of neuroblastoma, retinoblastoma, glioblastoma [or] and oligodentroglioma.

13. (Amended) A method for [treating] treatment of neoplastic diseases in a human in need of such treatment, which comprises administering to [a] said human an effective amount of an arsenic compound, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of at least one other therapeutic agent.

14. (Amended) The method of claim [12] 13 in which said other therapeutic agent is a chemotherapeutic agent or radiotherapeutic agent.

15. (Amended) The method of claims 1, 2, 3, or [12] 13 in which said administration is made parenterally, topically, dermally, directly into the tumor or orally.

16. (Amended) The method of claim [12] 13 in which said other therapeutic agent is selected from the group consisting of etoposide, cisplatin, carboplatin, estramustine phosphate, vinblastine, methotrexate, hydroxyurea, cyclophosphamide, doxorubicin, 5-fluorouracil, taxol, diethylstilbestrol, VM-26 (vumon), BCNU, all-trans retinoic, acid, procarbazine, cytokines, and therapeutic vaccines[, and other immunomodulators].

17. (Amended) The method of claim 1, 2, 3 or [12] 13 in which said administration is made via an implantation device.

18. (Amended) A method of [treating] treatment of hematopoietic disorders in a [mammal] human in need of such treatment, which comprises administering one or more arsenic compounds to said [mammal] human, wherein said hematopoietic disorder is selected from the group consisting of acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, myeloid metaplasia, myeloid dysplastic syndrome, multiple myeloma and plasmacytoma.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No: 077319/0225

In re patent application of
ELLISON, R. *et al.*

Serial No.: 09/173,531

Group Art Unit: 1616

Filed: October 15, 1998

Examiner: J. Pak

For: ***COMPOSITIONS AND METHODS FOR THE TREATMENT OF PRIMARY AND METASTATIC NEOPLASTIC DISEASES USING ARSENIC COMPOUNDS***

8-25-01

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 CFR §1.111

Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Official Action mailed March 21, 2001, the period for response to which has been extended to expire on August 21, 2001, by virtue of the accompanying petition and fee, applicants request that the PTO amend the above-identified application, as indicated below, and reconsider this case in light of the following remarks.

IN THE CLAIMS

Please cancel claims 19 and 20 and enter the following amended versions of claims 1, 2, 3, 9, 13, 14, 16 and 18 into the record.

SUB B1

1. (Amended) A method of treatment of solid tumors in a human in need of such treatment, which comprises administering a therapeutically effective amount of one or more arsenic compounds to said human.

2. (Amended) A method of treatment of metastatic neoplastic disease in a human in need of such treatment, which comprises administering a therapeutically effective amount of one or more arsenic compounds to said human.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	: Application of	: Group Art Unit 1616
	: T. Zhang	:
	:	: Examiner: J. Pak
Appln. No.	: 08/702,011	:
	:	:
Filed	: August 23, 1996	:
	:	:
For	: AN INJECTABLE	: Attorney Docket
	: COMPOSITION FOR CANCER	: No.: 3129-4000
	: TREATMENT	:

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION OF GUO-QIANG CHEN, M.D., Ph.D. UNDER 37 C.F.R. § 1.132

I, Guo-Qiang Chen, M.D., Ph.D., declare that:

1. I am a physician-scientist currently studying the use of arsenic trioxide to treat blood cancers, especially acute promyelocytic leukemia (APL).

2. I received a B.S. in Medicine from Hengyang Medical College in 1985; an M.S. in Pathophysiology at Shanghai Second Medical University in China in 1988; and an M.D./Ph.D. in Hematology at Shanghai Second Medical University in 1996.

3. I am presently an Associate Professor and Vice-Director of the Department of Biology at the Institute of Hematology of Rui-Jin Hospital; a Vice-Director of the Department of Biology at Shanghai Second Medical University; and a Visiting Research Assistant Professor at the Mount Sinai School of Medicine in New York. I have been studying and working in the scientific and/or medical field for almost 20 years.

4. During my career, I have received the following awards and honors: (1) the 1996 Award for Outstanding Young Scientific Phosphor of Shanghai Municipality; (2) the 1997

Award for Outstanding Young Scientist from the National Natural Sciences Foundation of China; and (3) the 1997 First Degree Award for the Progress in Sciences and Technologies of Shanghai Municipality.

5. I have authored and co-authored many scientific publications relating to the use of arsenic compounds for the treatment of APL in various journals. Some of these publications include: (1) Chen et al., In vitro studies on cellular and molecular mechanisms of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia: As_2O_3 induces NB4 cell apoptosis with down-regulation of Bcl-2 expression and modulation of PML-RARA/PML Protein. Blood 1996; 88:2025; (2) Chen et al., Pharmacokinetics and efficacy of low-dose all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Leukemia 1996; 10: 825; and (3) Su-Yin Zhang et al., Establishment of a human acute promyelocytic leukemia-ascites model in SCID mice. Blood 1996; 87: 3404.

6. I am familiar with the subject matter of the above-referenced patent application, which teaches pure arsenic trioxide being administered intravenously to treat APL. I further understand that the claims of the application have been rejected under 35 U.S.C. § 103 on the grounds of obviousness largely in view of the Sun et al. reference titled, "Use of Ai-Ling No.1 injection combined with pattern identification theory of Chinese traditional medicine, in the treatment of acute promyelocytic leukemia: Report from 32 patients."

7. At the Shanghai Institute of Hematology at Rui-Jin Hospital and Shanghai Second Medical University, where I am a Professor, we have received international recognition for a series of achievements, including the discovery of all-trans retinoic acid as a treatment for leukemia. During the past six years, I have directed bedside and bench studies on the use of arsenic trioxide (AT) to treat blood cancers, especially acute promyelocytic leukemia (APL). Actually, I was the responsible author of the August, 1996 publication in the journal, Blood, that made AT attract worldwide interest for cancer therapy. Therefore, I believe that I understand clearly the history and recent progress on the application of AT in the treatment of APL. In addition, I am familiar with Dr. Tingdong Zhang and his experimentation and teachings on the treatment of APL.

8. In the early 1970's when China was in the so-called "Cultural Great Revolution,"

many doctors were recalled into the countryside to provide medical services for farmers. As a director of such a team, Dr. Zhang of Harbin Medical University found that some rural doctors used "xinshi" (arsenic stone in English) and herbal concentrates to treat some cancers; some indefinitive effectiveness in such treatment was demonstrated. Thereafter, Dr. Zhang and his colleagues returned to study the use of AT to treat cancers.

9. First, Dr. Zhang and his colleagues prepared a solution called "Ai-Ling No. 1" (meaning in Chinese "the most effective drug for treatment of cancers"), which were crude extracts at least containing arsenic stone or arsenic sublimate and HgCl. With about 20 years of experimentation, they published the first short report in the Chinese Journal of Integration of Chinese and Western Medicine in 1992 (the Sun et al. reference). In this paper, they showed that Ai-Ling No. 1 combined with other Chinese herbs, such as Ginseng White Tiger Decoction and others, induced cancer remission in 21 of 32 APL patients. The specific role of arsenic still remained unknown. Subsequent studies showed that the HgCl component has little value other than increasing the toxicity of this treatment. Therefore, Dr. Zhang began to change the composition of Ai-Ling No. 1. In early 1996, he first reported in the Chinese Journal of Hematology that intravenous infusion of pure arsenic trioxide could effectively treat APL. Zhang was awarded a Chinese patent in 1999 for that discovery, from a patent application corresponding to the above-referenced application.

10. It should be emphasized that the original Ai-Ling No. 1 formulation is different from the currently used drug, pure arsenic trioxide. According to the Chinese Drug Dictionary, Xin-shi, the main composite of Ai-Ling No. 1, is a mixture of arsenolium and arsenopyritum. This is mainly composed of As406 mixed with ferric and sulfite. At the time of Dr. Zhang's invention, Xin-Shi was considered to be toxic and was used only in topical form. Therefore, in my professional opinion, the prevalent teaching at that time, including the Sun et al. reference, was not to develop and use arsenic in any form without additives, but to administer it along with detoxifying herbs.

11. Dr. Zhang's development of pure arsenic trioxide went against the teaching in the prior art at that time in China and elsewhere. Although Ai-Ling No. 1, with the herbal concentrates, was effective in treating APL at least as early as 1992, it was not clear what the

active ingredient was. Thus, in my professional opinion, there was no motivation at that time to use a pure form of arsenic without Chinese herbs/additives for the intravenous treatment of APL. In the face of the conventional wisdom at that time, Dr. Zhang is credited with the discovery of such an intravenous use of arsenic trioxide.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

01/03/01
Date

Chengaoqiang
Guo-Qiang Chen, M.D., Ph.D.